February 22, 2012

Genetic Maker of Men Is Diminished but Holding Its Ground, Researchers Say

By NICHOLAS WADE

Men, or at least male biologists, have long been alarmed that their tiny Y chromosome, once the same size as its buxom partner, the X, will continue to wither away until it simply vanishes. The male sex would then become extinct, they fear, leaving women to invent some virgin-birth method of reproduction and propagate a sexless species.

The fear is not without serious basis: The Y and X chromosomes once shared some 800 genes in common, but now, after shedding genes furiously, the Y carries just 19 of its ancestral genes, as well as the male-determining gene that is its raison d'être. So much DNA has been lost that the chromosome is a fraction of its original size.

But there are grounds for hope that the Y chromosome has reached a plateau of miniaturized perfection and will shrivel no more. Researchers led by Jennifer F. Hughes and David C. Page of the Whitehead Institute in Cambridge, Mass., have reconstructed the Y chromosome's past and find that its gene-shedding days seem to be over. Men are not living on borrowed time after all, they reported on Wednesday in the journal Nature.

In people, sex is determined by a single gene that resides on the Y chromosome. Chromosomes come in pairs, with one set bequeathed by each parent, and the Y is paired with X such that men have an X-Y pair and women an X-X. When the male-determining gene first arose, some 320 million years ago, the X and Y were both full-length chromosomes, each bearing the same set of 1,000 or so genes.

The Y chromosome began its self-sacrificing downsizing in the gallant cause of protecting women. As is well known, the purpose of sex is to exchange DNA between the mother's and father's version of each gene, creating novel combinations that will help children adapt to a new environment better than their parents did. So before generating sperm and eggs, the two members of each pair of chromosomes line up side by side and swap large chunks of DNA.

But the male-determining gene on the Y cannot be allowed to sneak across onto the X because it would insert maleness where it should not be. So a no-swapping zone was created around the male-determining gene. That inhibitory zone was extended in five stages until it covered the whole of Y chromosome except its very tips.

Genes at the tips of the Y exchange DNA with the X in the usual way, but all those in between were condemned to a monklike existence. And being unable to innovate, most of these genes became first antiquated and then dispensable. The X chromosome now has 790 genes in its no-swap zone, according to best current estimates, but the Y retains a mere 19 of these original genes.

As the only part of the human genome that never passes through a woman's body, the Y is the ideal refuge for male-favoring genes, especially those having to do with sperm production. Eight such genes have leapt onto the Y from other chromosomes, bringing its total score to 27. But these few additions have not allayed concern about the chromosome's long-term viability.

The Whitehead team's new report provides solid assurance by showing that the Y's shedding of genes is not a continuing process. Almost all of its genetic self-sacrifice occurred in the distant past.

This insight was gained by decoding the Y chromosome of rhesus monkeys, which shared a common ancestor with humans at the time, and retain 20 ancestral genes, meaning those that have a counterpart gene on the X. Only one of these genes has been lost in humans at some time in the last 25 million years, showing that the Y chromosome became essentially stabilized long ago.

"It's my sincere hope that this article might put the notion of the disappearing Y chromosome to rest," Dr. Page said.

He and his colleagues have reconstructed the entire history of the Y chromosome, showing that its no-swap zone expanded in five stages, of which the first began 320 million years ago and the last ended 29 million years ago. Each stage was caused when a chunk of DNA fell out of the Y chromosome and was accidentally flipped the wrong way when it was patched back in, so it would no longer line up correctly with its counterpart region on the X. At each stage, loss of genes was precipitous at first but then leveled off.

The first stage originated to fence in the male-determining genes. The driving force for creating more no-swap zones was probably the existence of genes in nearby regions that were beneficial for males and detrimental for females, Dr. Page said. Sexually antagonistic genes probably exist throughout the genome, but only on the Y chromosome can the male-favoring ones gain protection.